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ORIGINAL RESEARCH

Blood transfusion and oxygen extraction ratio in patients admitted to the general intensive care unit: A quasi experimental study

Transfusion sanguine et ratio d'extraction de l'oxygène chez des patients admis en unité de soins intensifs généraux: Une étude quasi expérimentale

Vitalis Mung'ayi, Thikra Sharif, David Samuel Odaba *

Department of Anaesthesia, Aga Khan University Hospital, Nairobi, Kenya

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Introduction: Blood transfusion is commonly undertaken in critically ill patients; and studies have suggested the use of oxygen extraction ratio (O_2ER) as an additional transfusion trigger in critically ill patients. The aim of this study was to establish the relationship between blood transfusion and oxygen extraction ratio in adult patients admitted to the general intensive care unit, using central venous oxygen saturation instead of mixed venous oxygen saturation.
Methods: Arterial and central venous blood samples were drawn and a blood gas analysis immediately before commencement of blood transfusion was undertaken. At least 15 min after completion of the transfusion, similar samples were drawn and the blood gas analysis was repeated. The O_2ER before and after transfusion was then calculated. Using paired student's *t*-test, we checked whether the mean difference between the two O_2ERs was statistically significant.
Results: We enrolled 58 patients in the study, the mean (±SD) haemoglobin concentration before transfusion was 7.38 g/dl (±1.71). The mean change in haemoglobin concentration following blood transfusion was 2.29 g/dl (±1.18), after transfusing an average of 1.95 (±0.83) units of packed cells. Mean O_2ER was 0.27 (±0.11) before, and 0.25 (±0.12) after RBC transfusion. The mean change in O_2ER was −0.018 SD ± 0.10 (95% CI, −0.043–0.007; $P = 0.15$). Linear regression analysis showed no statistically significant relationship between change in haemoglobin concentration and change in O_2ER; *p*-value = 0.12.
Discussion: The change in oxygen extraction ratio was not statistically significant following blood transfusion in adult patients admitted to the general ICU at a tertiary teaching hospital. Further studies are required especially in patients with increased pre transfusion O_2ER to evaluate the usefulness of this measurement as a possible transfusion trigger.

Introduction: La transfusion sanguine est effectuée de façon courante chez les patients en état critique ; et des études ont suggéré l'utilisation du ratio d'extraction de l'oxygène (REO_2) comme déclencheur supplémentaire d'une transfusion chez les patients en état critique. Le but de cette étude était de déterminer le lien entre transfusion sanguine et ratio d'extraction de l'oxygène chez les patients adultes admis en unité de soins intensifs généraux en utilisant la saturation veineuse centrale en oxygène au lieu de la saturation veineuse mixte en oxygène.
Méthodes: Des échantillons sanguins artériels et veineux centraux ont été prélevés et une analyse des gaz du sang a été effectuée juste avant le commencement de la transfusion sanguine. Au moins 15 min après l'achèvement de la transfusion, des échantillons similaires ont été prélevés et l'analyse des gaz du sang à nouveau effectuée. Le REO_2 avant et après la transfusion a ensuite été calculé. En utilisant des tests de Student appariés, nous avons vérifié si la différence moyenne entre les deux REO_2 était statistiquement significative.
Résultats: Nous avons inclus 58 patients dans l'étude, le taux moyen (±écart-type) d'hémoglobine avant la transfusion était de 7.38 g/dl (±1.71). Le changement moyen de taux d'hémoglobine à la suite de la transfusion sanguine était de 2.29 g/dl (±1.18), après avoir transfusé une moyenne de 1.95 (±0.83) unités de globules concentrés. Le REO_2 moyen était de 0.27 (±0.11) avant, et de 0.25 (±0.12) après la transfusion de globules rouges. Le changement moyen de REO_2 était de −0.018, l'écart-type de ±0.10 (intervalle de confiance de 95%, −0.043–0.007; $P = 0.15$). Une analyse de régression linéaire n'a montré aucun lien statistiquement significatif entre le changement du taux d'hémoglobine et le changement de REO_2; $p = 0.12$.
Discussion: Le changement du ratio d'extraction de l'oxygène suite à une transfusion sanguine n'était pas statistiquement significatif chez les patients adultes admis aux soins intensifs généraux dans un centre hospitalier universitaire. Des études supplémentaires sont nécessaires surtout chez les patients dont le REO_2 avant la transfusion a augmenté afin d'évaluer l'utilité de cette mesure comme déclencheur possible d'une transfusion.

African relevance

- Minimising unnecessary blood transfusion by using accurate transfusion triggers may ensure appropriate use of a scarce resource.
- Samples from central venous catheters can be used to measure central venous oxygen saturation.
- Oxygen extraction ratio is a useful, additional transfusion trigger to haemoglobin when deciding on blood transfusion.

* **Correspondence to David Samuel Odaba**. david.odaba@live.co.uk

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Introduction

Little is known about oxygen extraction ratio and its relationship with anaemia and red blood cell (RBC) transfusion, as well as its ability to potentially supplement haemoglobin (Hb) concentration as a transfusion trigger. Oxygen extraction ratio (O_2ER) is the amount of oxygen consumed (VO_2), as a fraction of oxygen delivered (DO_2); the latter being a product of cardiac output (CO) and arterial oxygen content (CaO2).[1] VO_2 is essentially the difference between CaO_2 and venous oxygen content (CvO_2); CvO_2 being determined mainly by the Hb concentration and mixed venous oxygen saturation (SvO_2), while CaO_2 is determined by Hb concentration and arterial oxygen saturation (SaO_2).[1] Orlov et al. examined temporal changes in Hb concentration and O_2ER following RBC transfusion post cardiac surgery with cardiopulmonary bypass, and suggested that; O_2ER, a readily available index of systemic oxygenation may be used to supplement Hb concentration as a RBC transfusion trigger.[2]

Oxygen extraction ratio is used as a marker for tissue oxygen extraction, and is expected to increase in the presence of either increased VO_2 or decreased DO_2. A reduction in DO_2 may be due to decreased CaO_2 from anaemia and/or low SaO_2, while an increase in VO_2 may be due to stress, fever, shivering and pain.[2,3] Studies have shown that oxygen extraction ratio can be used to supplement haemoglobin concentration as a trigger for blood transfusion in ICU patients[4,5]; however, for purposes of measuring SvO_2, these studies involved placement of a Swan-Ganz catheter which requires technical expertise. In addition, the benefit of inserting a Swan-Ganz catheter in critically ill patients is still questionable.[6]

To the best of our knowledge, no published study has investigated the value of using blood samples from the central venous catheter to measure central venous oxygen saturation ($ScvO_2$) for purposes of calculating the oxygen extraction ratio; despite oxygen saturations in this samples showing good correlation with those from the pulmonary artery (SvO_2), drawn via the pulmonary artery catheter.[6–8]

The purpose of our study therefore, was to investigate how blood transfusion affects O_2ER in adult patients admitted to the general ICU at a tertiary teaching hospital; using $ScvO_2$ instead of SvO_2 in the calculation of O_2ER.

Methods

The study was undertaken in the ICU at the Aga Khan University hospital, Nairobi; between July 2011 and January 2012. We obtained written approval from the institution's research and ethics committee followed by written informed consent from patients themselves whenever possible; or from the next of kin as indicated in the hospital records; and in adherence to the declaration of Helsinki. The study was funded by the postgraduate medical education programme through the department's budget. Patients were included if they underwent blood transfusion (packed red blood cells or whole blood), were aged above 18 years and a written informed consent was given, had a mean arterial blood pressure (MAP) not less 65 mmHg and an hourly urine output of at least 0.5 mls/kg. The exclusion criteria included age below 18 years, MAP below 65 mmHg, oliguria, on-going haemorrhage, congestive heart failure, carbon monoxide or cyanide poisoning and shock of any origin. Since there are no blood transfusion protocols in place, the attending physician for each patient made all RBC transfusion decisions; based on his or her own judgement. Patient's age, gender and physiological parameters (temperature, mean arterial blood pressure, heart rate and central venous pressure) were collected in all study patients as per protocol.

The number of units of blood (packed cells or whole blood) transfused per study patient during the study period was recorded. The reasons for the blood transfusion, the Hb concentration and O_2ER immediately before and a minimum of 15 min after the end of the blood transfusion were subsequently recorded.[9,10] If a patient was scheduled to receive more than 1 unit of packed cells, the Hb and O_2ER were recorded immediately before commencing the first unit and at least fifteen minutes after completion of the last unit.

To calculate O_2ER, blood gas analysis on samples obtained from indwelling arterial and central venous catheters was undertaken. The primary outcome was the change in O_2ER following blood transfusion; while our secondary outcomes were: how the APACHE II score on admission correlated with the change in O_2ER after blood transfusion and the effect of haemoglobin concentration on O_2ER.

All blood samples were analysed using the blood gas analyser located in a centralised room within the ICU (RADIOMETER COPENHAGEN ABL-800 BASIC). The study was registered with the pan African clinical trials register; PACTR: 201109000317141.

We determined that a sample size of 58 patients undergoing blood transfusion would be sufficient to estimate the mean percentage (%) change in oxygen extraction ratio within ± 2 of the true value with 95% confidence.[2] Data analysis was undertaken using the SPSS statistics 17.0 software (IBM Corporation). The oxygen extraction ratio before and after transfusion was compared using paired student's *t*-test, while linear regression analysis was used to analyse the relationship between changes in haemoglobin concentration and oxygen extraction ratio. Data are presented as mean ± standard deviation unless otherwise specified, and a p-value < 0.05 was considered to be statistically significant.

Results

A total of fifty-eight patients were included in the study; 36 (62.1%) were non-surgical patients while 22 (37.9%) were surgical (post-operative). The patient's baseline characteristics are summarised in Table 1. Measured clinical variables pre and post blood transfusion are summarised in Table 2.

The mean haemoglobin concentration before blood transfusion was 7.37 g/dl (SD 1.71) with the lowest being 3 g/dl and the highest being 14 g/dl. Post blood transfusion, the mean haemoglobin concentration was 9.67 g/dl (SD 1.68), with the lowest being 5 g/dl and the highest being 15 g/dl. The average number of packed red blood cell units transfused per patient was 1.95 (with a range between 1 and 5 units); no patient was transfused with whole blood. The mean change in haemoglobin concentration was 2.29 g/dl (SD 1.18). The lowest increase in haemoglobin concentration was by 1 g/dl while the highest increase in haemoglobin concentration was by 6 g/dl. The mean (SD = 0.10) difference in the pre and post

Table 1 Patients' baseline characteristics ($n = 58$).

Characteristic	Mean	SD
Age (years)	60.7	16.7
APACHE II score	18.9	9.5
Temperature (°C)	37.0	0.6
MAP (mmHg)	76.9	10.1
HR (beats/min)	98.1	16.5
CVP (cmH_2O)	14.4	5.7

SD, standard deviation; APACHE, acute physiology and chronic health evaluation; MAP, mean arterial pressure; mmHg, millimetres of mercury; HR, heart rate; CVP, central venous pressure; cmH_2O, centimetres of water.

Table 2 Clinical variables ($n = 58$).

Variable	Mean	Std. deviation
Units of blood transfused	1.95	0.83
Hb before transfusion (g/dl)	7.37	1.71
Hb after transfusion (g/dl)	9.67	1.68
Change in Hb concentration	2.29	1.18
SaO_2 before transfusion	0.96	0.03
$ScVO_2$ before transfusion	0.70	0.11
SaO_2 after transfusion	0.96	0.03
$ScVO_2$ after transfusion	0.72	0.12
O_2ER before transfusion	0.27	0.11
O_2ER after transfusion	0.25	0.12

Hb, haemoglobin; g/dl, gram per decilitre; SaO_2, arterial oxygen saturation; $ScVO_2$, central venous oxygen saturation; O_2ER, oxygen extraction ratio.

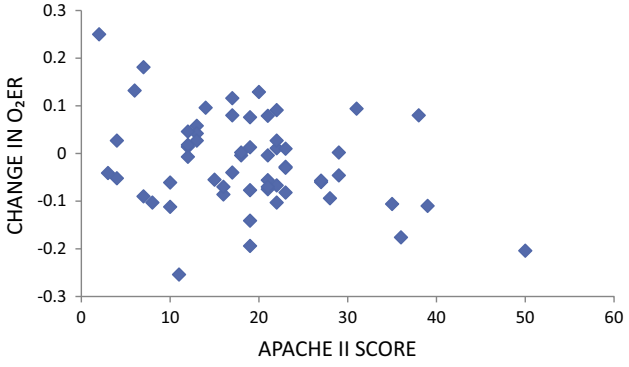

Figure 1 The relationship between changes in O_2ER and APACHE II.

transfusion O_2ER was –0.018 (95% CI, −0.043–0.007; $P = 0.15$). Out of the 58 patients transfused, only 23 patients (39.7%) had an O_2ER above 0.30 which is regarded as the upper limit of the normal 2. Sub group analysis of these 23 patients yielded a mean reduction of O_2ER of 0.055 (SD 0.11; p-value of 0.02).

Linear regression analysis showed no statistically significant relationship between change in Hb concentration and change in O_2ER with a p-value of 0.119. Further regression analysis

Table 3 Linear regression output for change in O_2ER compared to various patient variables.

Variable	*B*	SE	ß
Constant	0.08	0.78	
Hb	−0.02	0.01	−.20
Age	−0.0004	0.001	−.07
Sex	0.002	0.03	.01
APACHE II	−0.003	0.001	−.31*
Temperature	−0.0002	0.02	−.001
MAP	0.0002	0.001	.03
CVP	0.001	0.002	.04

Note: $R^2 = 0.15$ ($p = 0.28$).
* $p < 0.05$; SE, standard error; Hb, haemoglobin; APACHE, Acute Physiology And Chronic Health Evaluation; MAP, mean arterial pressure; CVP, central venous pressure.

that included other variables (age, sex, APACHE II score, temperature, MAP, and CVP) in addition to O_2ER did not show any statistically significant relationship, with the exception of the APACHE II score which had a p-value of 0.036 (Fig. 1 and Table 3). Patients with higher APACHE II scores on admission had a larger reduction in O_2ER compared to those with a lower score.

Discussion

In this study, blood transfusion did not significantly change the oxygen extraction ratio in adult patients admitted to the general ICU at a tertiary teaching hospital. Furthermore, change in haemoglobin concentration following blood transfusion and change in the oxygen extraction ratio did not correlate. There was a statistically significant relationship (p-value of 0.036) between the APACHE II score and the change in oxygen extraction ratio following blood transfusion; however, our study was not adequately powered to assess the significance of this finding, raising the need for further studies in this area.

These findings suggest lack of significant improvement in tissue oxygenation, despite the increase in oxygen content that arose after increasing haemoglobin concentration by transfusing red blood cells. However, there was a trend suggesting benefit from RBC transfusion in patients who had a higher APACHE II score at admission. O_2ER reduced by 0.02 but still remained within the normal range of 0.25–0.30, meaning the body may have adjusted its O_2ER in the presence of increased oxygen delivery (DO_2) to maintain oxygen consumption (VO_2) constant.

All the blood transfusions administered during the study period, were based on haemoglobin concentration regardless of what the oxygen extraction ratio was. Sub group analysis of the patients who had a pre-transfusion O_2ER of more than 0.30 yielded a mean reduction in O_2ER of 0.055 (SD 0.11; p-value of 0.024). This may imply that majority of the patients who were transfused (60.3%), did not physiologically require RBC transfusion, and so did not benefit from the increased oxygen content. Orlov et al. in their study demonstrated that O_2ER does not significantly change after blood transfusion if the baseline value was normal.[2] It is therefore possible that lack of a significant change in the O_2ER in our study resulted

from the fact that about 60% of the patients had a baseline O_2ER below 0.30.

Sehgal et al. demonstrated that using O_2ER as a transfusion trigger could potentially reduce the number of blood transfusions.[4] They showed that if they had used an O_2ER of 0.50 as the transfusion trigger, then only 7 out of 41 patients in the transfusion group would have been transfused. Since they planned to account for the possibility of patients being unable to increase their cardiac output as a compensatory mechanism, they settled on a transfusion trigger of 0.45; this resulted in doubling of the number of patients who would be transfused. In this study therefore, if we utilised a transfusion trigger O_2ER of 0.45, then only 3 out of the 58 patients would have been transfused.

It is important to note that unlike the two studies quoted above, we used central venous oxygen saturation. Scheinman et al. demonstrated that mean central venous oxygen saturation ($ScvO_2$) was significantly greater than mean mixed venous oxygen saturation (SvO_2) by about 5%.[6] $ScvO_2$ is measured in blood sampled from the superior vena cava (SVC), which contains venous blood, from the upper body (head, neck, upper limbs and upper trunk). Blood from the lower body (intra-abdominal organs and lower limbs) drains via the inferior vena cava (IVC) and has slightly higher oxygen saturation due to the high venous oxygen saturation in the renal veins.[6,11] SvO_2 is measured in blood sampled from the pulmonary artery, which is a mixture of blood from both the SVC and IVC; this explains the variation in values of SvO_2 and $ScvO_2$.[11] The same study by Scheinman et al. also showed that good correlation existed between changes in central venous and mixed venous oxygen saturations; however, this difference in saturations increased to a mean of about 10% in those patients who either had heart failure or shock.[6]

Because our study was carried out in a general ICU and we utilised central venous and not mixed venous blood samples to calculate oxygen saturation, we might consider a much lower O_2ER as a possible trigger for blood transfusion. Despite the fact that we excluded patients in heart failure or shock, reducing the trigger O_2ER from 0.45 as observed by Sehgal and coworkers[4] to 0.35 in this study would have resulted in only 13 patients being transfused; thereby reducing the number of patients transfused by 78%.

As much as this was a physiological study without any consideration for clinical outcomes, several authors have demonstrated in previous studies that blood transfusion is associated with poor outcomes in critically ill patients[12–15]; therefore, a reduction in blood transfusion of this magnitude as demonstrated above, is likely to be associated with clinical benefits in this group of patients.

Potential confounders include: RBC storage lesions, arterial blood pH, and accuracy of O_2ER in ICU patients; all of which might affect the findings of this study. During storage, RBC's undergo a series of changes that reduce their survival and function; the so called "storage lesions".[16] There is a reduction in 2,3-diphosphoglycerate (2,3-DPG) in RBC's after 48 h of storage, leading to impaired unloading of oxygen to the tissues.[16] Several studies have however disputed the clinical significance of the reduction in 2,3-DPG levels in stored blood. Weiskopf et al. in their study concluded that, despite erythrocytes stored for 3 weeks in citrate phosphate dextrose adenine (CPDA) being depleted of 2,3-DPG with reduction in their P50 (the partial pressure of oxygen in the blood at which the haemoglobin is 50% saturated), they still release adequate oxygen to reverse the deficits of acute anaemia to an extent equivalent to that of erythrocytes with a normal P50.[17] Orlov et al. further demonstrated that there was no latency in oxygenation following red blood cell transfusion.[1] In our study, post transfusion O_2ER was undertaken at least 15 min after completion of blood transfusion, it is therefore unlikely that depletion of 2,3-DPG contributed significantly to the calculated value.

The other possible confounder which may have affected the oxyhaemoglobin dissociation curve is the arterial pH. Alkalosis would result in a leftward shift of the oxyhaemoglobin dissociation curve (decreased P50) causing reduced dissociation of oxygen from haemoglobin. Acidosis would have had the opposite effect. In this study, since each patient was acting as their own control, the resulting effect would have equally affected both the pre and post transfusion O_2ER. This would therefore have had no effect on the change in the O_2ER following RBC transfusion. However, we cannot completely rule out the effect of pH because the duration of blood transfusion varied in each patient; and the pH may have changed during that period in some patients. A controlled study may eliminate this confounder.

Another argument is with regard to how useful oxygen extraction ratio is in ICU patients. It is thought that O_2ER is impaired during critical illness.[18] Several studies have supported this hypothesis by showing that there is lactic acidosis in critically ill patients despite an increased oxygen delivery; implying anaerobic metabolism is required despite increased oxygen supply.[19,20] It had therefore been concluded that oxygen consumption (VO_2) could be pathologically dependent on delivery (DO_2) in critically ill patients,[21] and that ineffective oxygen extraction maybe due to either poor oxygen uptake or poor utilisation by the cells;[22] However, both VO_2 and DO_2 in the these studies were calculated, and this may have introduced mathematical coupling errors which could falsely increase the strength of the relationship between VO_2 and DO_2. This led to subsequent studies which measured VO_2 and DO_2 independently.[18,23,24] Bruining et al. demonstrated in their study that, in a certain group of patients (septic and postoperative), there is a minimal positive relationship between VO_2 and DO_2.[21] They therefore concluded that in this group of patients who are haemodynamically stable, VO_2 might not be pathologically dependent on DO_2; and that lactic acidosis does not necessarily mean the presence of an oxygen debt. Michelle et al. further demonstrated that increasing DO_2 did not improve outcome, and that it was followed by a fall in oxygen extraction.[25]

It is therefore possible that DO_2 and VO_2 relate similarly in both critically ill and healthy patients; and that increased oxygen extraction, and not increased DO_2, have the greatest impact in increasing VO_2 in critically ill patients. The value of O_2ER that we calculated in this study may therefore be a fair reflection of the VO_2 based on the DO_2, regardless of patients' lactate level since we excluded patients who were haemodynamically unstable.

One of the strengths of this study is the fact that to the best of our knowledge, it is the first to evaluate the usefulness of using blood samples from the central venous catheter in calculating the O_2ER with the aim of using it as a possible transfusion trigger. In addition, this study was undertaken in a general ICU which is the common set up in most Third

World countries and therefore the results would be recommended for this setting.

Limitations of this study include: being a single centre study involving a small number of patients; and luck of a homogenous study population; also, although O_2ER is a useful marker of global oxygenation, it does not accurately reflect individual organ and tissue oxygenation; therefore, a low O_2ER may not necessarily mean RBC transfusion is not required. Finally, most RBC transfusions were carried out when patient's haemoglobin concentration was above 7.0 g/dl. This limited our ability to assess adequately how O_2ER changes in patients whose transfusion is based on a haemoglobin concentration below 7 g/dl as suggested by the TRICC trial.[2]

Conclusion

In this study, we concluded that the change in oxygen extraction ratio was not statistically significant following red blood cell transfusion in patients admitted to the general ICU at a tertiary teaching hospital. Further studies are required especially in patients with increased pre transfusion O_2ER to evaluate the usefulness of this measurement as a possible transfusion trigger.

Conflicts of interest

The authors declare no conflict of interest.

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